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(71) Applicant (for all designated States except US): MUSC FOUNDATION FOR RESEARCH DEVELOPMENT [US/US]; P.O. Box 250194, Charleston, SC 29425 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): DONG, Jian-Yun [—/US]; 4201 Victory Pointe Dr., Mt. Pleasant, SC 29466 (US). RUBINCHIK, Semyon [—/US]; 811 E. Hideaway Bay Lane, Mt. Pleasant, SC 29464 (US). WORARATANADHARM, Jan [—/US]; 411 Meeting St., #5102, Charleston, SC 29403 (US).

(74) Agent: KRAWZSENEK, Michael, R.; Fulbright & Jaworski LLP, 600 Congress Avenue, Suite 2400, Austin, TX 78701 (US).

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2

**(54) Title: AN AUTOLOGOUS UPREGULATION MECHANISM ALLOWING OPTIMIZED CELL TYPE-SPECIFIC AND REGULATED GENE EXPRESSION CELLS**

WO 2004/099377

**(57) Abstract:** The present invention provides methods for high level, regulated transgene transcription that is restricted to cell populations of specific types. The process is designed to work with any inducible expression regulation systems, adapting them to a tissue-specific expression pattern while simultaneously delivering maximal achievable expression levels. In particular, the invention utilizes hybrid promoters that contain the DNA elements for both cell type-specific and regulated transcription. By placing the gene of the transcriptional activation factor (TAF) under the control of this tissue-specific/drug-regulated (TSDR) promoter, this invention achieves high expression levels of TAF in specific target cells by first initiating TAF expression using cell-type specific transcription elements, and subsequently amplifying transcriptional activity by establishing an autoregulatory positive feedback loop. In non-target cells, cell type-specific elements of the TSDR promoter will be inactive, the TAF expression will not be initiated, and auto-upregulation will not occur. For cell type-specific promoters with leaky low-level activity in non-target cells, a variation of this system has been developed which combines autologous upregulation of TAF with the expression of cross-competing transcriptional silencers (TSi) to achieve a type of eukaryotic "genetic switch" - either shutting off transgene and TAF expression completely or promoting maximal expression levels, depending on the original activity level of the specific promoter in that particular cell.